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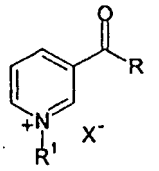
(54) Title: COMPOSITIONS FOR THE TREATMENT OF SKIN DISEASES



(I)

(57) Abstract

Disclosed is the use of a compound of formula (I) wherein R represents the group NR^2R^3 or the group OR^4; R^1 represents C_{1-4} alkyl; R^2 and R^4 each independently represent hydrogen or C_{1-4} alkyl; R^3 represents hydrogen, C_{1-4} alkyl or CH_2OH; and X^- is a physiologically suitable counter–anion; in the treatment of skin diseases or disorders, hair loss, sunburn, burns, scalds and for wound healing; also disclosed are pharmaceutical formulations of compounds of formula (I), particularly for topical use.

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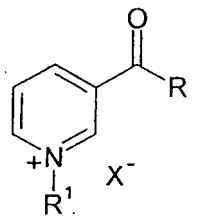
COMPOSITIONS FOR THE TREATMENT OF SKIN DISEASES

The present invention relates to methods and compositions for the treatment of skin diseases and disorders. In particular it relates to methods and compositions for the treatment of skin diseases and disorders in which oedema, erythema, cutaneous eruption, dilation of superficial blood vessels and desquamation are manifested (including when accompanied by pruritus and burning sensation), as well as in cases of intensified seborrhoea.

There are several topical therapeutic products in use, mostly containing corticosteroids, which exert anti-inflammatory, oedema-reducing, anti-seborrhoeic and anti-pruritic effects. Nicotinamide, i.e. vitamin PP is also administered in adjunctive medical treatment of skin diseases. There is also an ointment in use, known as "Dernilan", which contains nicotinamide, allantoin, salicylic acid and camphorae which exerts anti-inflammatory and exfoliating effects on the skin. The use of nicotinamide for the treatment of acne vulgaris is also disclosed in EP-A-0052705; the use of nicotinamide derivatives for the treatment of psoriasis is disclosed in US-A-4,067,975; and the use of certain nicotinamide and nicotinic acid derivatives for the treatment of various skin conditions is disclosed in WO-A-98/52927.

It has now, surprisingly, been found that 1-alkylnicotinamide salts and 1-alkylnicotinic acid ester salts can be used to treat a wide variety of skin diseases and disorders and that the use of these compounds provides certain advantages over the use of nicotinamide, in particular an increased efficacy at a specified dose and/or a reduction in undesirable side effects. In particular, topical treatment of skin diseases such as acnes by administering a solution of the 1-methylnicotinamide salts and 1-methylnicotinic acid ester salts of the present invention has been shown to produce at least a similar therapeutic effect at a concentration approximately 100 times lower than the corresponding treatment with nicotinamide or nicotinic acid respectively, but with no appreciable side effects.

Thus, according to one aspect of the present invention, there is provided a compound of formula (I):



(I)

wherein R represents the group NR^2R^3 or the group OR^4;

R^1 represents C_{1-4} alkyl;

R^2 and R^4 each independently represent hydrogen or C_{1-4} alkyl;

R^3 represents hydrogen, C_{1-4} alkyl or CH_2OH;

and X^- is a physiologically suitable counter-anion;

for use in therapy.

According to a further aspect of the present invention there is provided the use of a compound of formula (I) as defined above for the treatment of skin diseases or disorders.

According to a further aspect of the present invention there is provided the use of a compound of formula (I) as defined above for the treatment of hair loss, sunburn, burns, scalds and for wound healing.

According to a further aspect of the present invention, there is provided a compound of formula (I) as defined above, for use in the preparation of a medicament for the treatment of skin diseases or disorders.

According to a further aspect of the present invention, there is provided a compound of formula (I) as defined above, for use in the preparation of a medicament for the treatment of hair loss, sunburn, burns, scalds and for wound healing.

According to a further aspect of the present invention, there is provided a method of treatment of a skin disease or disorder in a human or animal subject, comprising the administration to said subject of an effective amount of a compound of formula (I) as defined above.

According to a further aspect of the present invention, there is provided a method of treatment of hair loss, sunburn, burns, scalds and for wound healing in a human or animal subject, comprising the administration to said subject of an effective amount of a compound of formula (I) as defined above.

In the compounds of formula (I), R^1 is preferably ethyl or methyl, more preferably methyl. Preferably R^2 represents ethyl, methyl or hydrogen, more preferably methyl or hydrogen, most preferably hydrogen. Preferably R^3 represents CH_2OH, methyl or hydrogen, more preferably CH_2OH or hydrogen, most preferably hydrogen. In a further preferment, R^4 represents C_{1-4} alkyl. In a further preferment R^4 represents propyl, ethyl, methyl or hydrogen, more preferably propyl, ethyl or methyl, most preferably propyl or ethyl. Preferably R represents the group NR^2R^3.

In an especially preferred embodiment of the present invention, the compound of formula (I) is a 1-methylnicotinamide salt, i.e. R^1 represents methyl, and R^2 and R^3 each represent hydrogen.

In a further especially preferred embodiment of the present invention, the compound of formula (I) is a 1-methyl-N'-hydroxymethylnicotinamide salt, i.e. R^1 represents methyl, R^2 represents hydrogen, and R^3 represents CH_2OH.

In a further especially preferred embodiment of the present invention, the compound of formula (I) is a 1-methylnicotinic acid salt, i.e. R^1 represents methyl, and R^4 represents hydrogen.

In a further especially preferred embodiment of the present invention, the compound of formula (I) is a 1-methylnicotinic acid ethyl ester or 1-methylnicotinic acid propyl ester salt, i.e. R^1 represents methyl, and R^4 represents propyl or ethyl.

As indicated above, X^- is any physiologically suitable counter-anion. The 1-alkylnicotinamide, 1-alkylnicotinic acid and 1-alkylnicotinic acid ester salts of the present invention can thus be derived from any physiologically acceptable acid, whether organic or inorganic in origin. Suitable inorganic acid salts include, for example, chloride, bromide, iodide and carbonate; suitable organic acid salts include mono-, di- and tri- C_{1-18} carboxylic acid salts, for example, acetate, benzoate, salicylate, glycolate, lactate, maleate and citrate. Preferred salts include chloride, benzoate, salicylate, acetate, citrate and lactate. Especially preferred are chloride salts.

Some of the compounds of formula (I) are commercially available, for example 1-methylnicotinamide chloride (Sigma) and 1-methylnicotinic acid chloride (Sigma). Alternatively, the compounds can be readily prepared from commercially available compounds (including nicotinamide and nicotinic acid) by synthetic methods well-known to

the person skilled in the art. Such methods would include synthesis from appropriately substituted pyridine compounds.

According to a further aspect of the present invention, there is provided a pharmaceutical formulation comprising a compound of formula (I) together with one or more pharmaceutically acceptable carriers, diluents or excipients.

In the treatment of skin conditions, it is possible to administer the compound of formula (I) orally in suitable formulations, preferably tablets or capsules. However, of particular utility are topical formulations of a compound of formula (I). The type of carrier utilised in the present invention depends on the type of product form desired for the composition. The topical compositions useful in the present invention may be made into a wide variety of product forms such as are known in the art. These include, but are not limited to, lotions, creams, gels, sticks, shampoos, soaps, sprays, ointments, pastes and mousses. These product forms may comprise several types of carriers including, but not limited to, solutions, aerosols, emulsions, gels, solids, and liposomes. Topical formulations are most suitably in the form of an ointment, gel, cream, shampoo, soap, spray, lotion or a solution.

The compound of formula (I) may be administered topically to the skin (including the scalp), or to the mucosal surfaces, for example by intranasal, oral, intravaginal or intrarectal administration. Preferred is topical administration to the skin at the location of the principal manifestation of the skin disease or disorder, the burn or wound.

The topical formulations of the present invention comprise a safe and effective amount of a dermatologically acceptable carrier within which the compound of formula (I) and other optional components are incorporated to enable the compound of formula (I) and other optional components to be delivered to the skin or other relevant site at an appropriate concentration. The carrier can thus act as a diluent, dispersant, solvent, or the like which ensures that the formulation can be applied to and distributed evenly over the selected target to provide an appropriate concentration of the compound of formula (I).

Preferred topical formulations according to the present invention comprise about 90 to 99.95% of a pharmaceutical base carrier and about 0.005 to about 10% by weight of a compound of formula (I) as defined above More preferably the topical formulation contains about 0.01 to about 10% by weight of a compound of formula (I). Preferred pharmaceutical base carriers are an ointment, gel, or aqueous solution. In an ointment the compound of

formula (I) is preferably present at a concentration by weight of 0.1 to 10%, more preferably 0.5 to 10%. In a gel the compound of formula (I) is preferably present in a concentration by weight of 0.05 to 2%, more preferably 0.05 to 1%, most preferably 0.1 to 0.5%. In a solution, the compound of formula (I) is preferably present in a concentration by weight of 0.005 to 0.1%, more preferably 0.005 to 0.05%, most preferably 0.01%.

The carrier may contain one or more dermatologically acceptable solid, semi-solid or liquid fillers, diluents, solvents, extenders and the like. The carrier may be solid, semi-solid or liquid. Preferred carriers are substantially liquid. The carrier can itself be inert or it can possess dermatological benefits of its own. Concentrations of the carrier can vary with the carrier selected and the intended concentrations of the compound of formula (I) and the other optional components.

Suitable carriers include conventional or otherwise known carriers that are dermatologically acceptable. The carrier should also be physically and chemically compatible with the compound of formula (I), and should not unduly impair stability, efficacy or other benefits associated with the formulations of the present invention. Preferred components of the formulations of the present invention should be capable of being comingled in a manner such that there is no interaction which would substantially reduce the efficacy of the formulation under ordinary use situations.

Preferred carriers contain a dermatologically acceptable, hydrophilic diluent. As used herein, "diluent" includes materials in which the compound of formula (I) can be dispersed, dissolved, or otherwise incorporated. Nonlimiting examples of hydrophilic diluents are water, organic hydrophilic diluents such as lower monovalent alcohols (e.g., C_1–C_4) and low molecular weight glycols and polyols, including propylene glycol, polyethylene glycol (e.g., Molecular Weight 200-600 g/mole), polypropylene glycol (e.g. Molecular Weight 425-2025 g/mole), glycerol, butylene glycol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, sorbitol esters, butanediol, ether propanol, ethoxylated ethers, propoxylated ethers and combinations thereof. Water is a preferred diluent. The composition preferably comprises from about 60% to about 99.99% of the hydrophilic diluent.

Solutions according to the subject invention typically include a dermatologically acceptable hydrophilic diluent. Solutions useful in the subject invention preferably contain from about 60% to about 99.99% of the hydrophilic diluent.

Aerosols according to the subject invention can be formed by adding a propellant to a solution such as described above. Exemplary propellants include chloro-fluorinated lower molecular weight hydrocarbons. Additional propellants that are useful herein are described in Sagarin, Cosmetics Science and Technology, 2nd Edition, Vol. 2, pp. 443-465 (1972), incorporated herein by reference. Aerosols are typically applied to the skin as a spray-on product.

The topical compositions of the subject invention, including but not limited to lotions and creams, may comprise a dermatologically acceptable emollient. Such compositions preferably contain from about 2% to about 50% of the emollient. Emollients tend to lubricate the skin, increase the smoothness and suppleness of the skin, prevent or relieve dryness of the skin, and/or protect the skin. Emollients are typically water-immiscible, oily or waxy materials. A wide variety of suitable emollients are known and may be used herein. Sagarin, Cosmetics Science and Technology, 2nd Edition, Vol.1, pp. 32-43 (1972), incorporated herein by reference, contains numerous examples of materials suitable as an emollient.

Lotions and creams according to the present invention generally comprise a solution carrier system and one or more emollients. Lotions typically comprise from about 1% to about 20%, preferably from about 5% to about 10%, of emollient; from about 50% to about 90%, preferably from about 60% to about 80%, water. A cream typically comprises from about 5% to about 50%, preferably from about 10% to about 20%, of emollient; and from about 45% to about 85%, preferably from about 50% to about 75%, water.

Ointments of the present invention may comprise a simple carrier base of animal or vegetable oils or semi-solid hydro-carbons (oleaginous); absorption ointment bases which absorb water to form emulsions; or water soluble carriers, e.g., a water soluble solution carrier. Ointments may further comprise a thickening agent, such as described in Sagarin, Cosmetics, Science and Technology, 2nd edition, Vol. 1, pp. 72-73 (1972), incorporated herein by reference , and/or an emollient. For example, an ointment may comprise from about 2% to about 10% of an emollient; and from about 0.1% to about 2% of a thickening agent.

Preferred ointments comprise Eucerine and glycerol; preferred gels comprise methylcellulose, glycerol and water, or comprise polyacrylic acid, polyethylene glycol,

ethanol, triethanolamine, paraben and water; preferred solutions comprise aqueous solutions or solutions of ethyl alcohol or propylene glycol.

In accordance with the invention, the compounds of formula (I) are useful for the treatment of skin disorders or diseases, including crural ulceration, acne juvenile, acne rosacea, psoriasis, atopic dermatitis and vitiligo.

In addition, the compounds of formula (I) have been shown to be useful in the treatment of hair loss, especially alopecia areata, androgenic alopecia, and alopecia caused as a side effect of chemotherapy or radiotherapy.

In addition, the compounds of formula (I) have been shown to be of use in the treatment of burns and scalds (particularly first and first/second degree burns and scalds) and in wound healing, as well as in treating sunburn.

A prophylactic or preventative capability of the compounds of formula (I) has also been shown for chronic and recurrent diseases such as, for example, psoriasis, leg ulcers or acne. The preventive effect consists in keeping the improvement of a previously healed status for a prolonged period of time after cessation of active pathological symptoms.

The compounds of formula (I) also show utility in cosmetology, in particular in providing regeneration and smoothing of the skin; thus treatment of skin ageing effects, such as wrinkles etc. is also contemplated by the present invention.

Additional excipients well known in the art can also be included in the formulations of the present invention; in particular, commonly used stabilisers may be advantageously included to allow the formulations to remain stable for a suitable period, for example, for up to 2 years.

According to a further aspect of the present invention there is also provided the use of compounds of formula (I) as defined above in combination with other therapeutically effective compounds used in the treatment of the skin disorders and diseases and other conditions referred to above. Also provided are formulations comprising a compound of formula (I) together with one or more of such other therapeutically effective compounds. Suitable other therapeutically effective compounds include, for example, vitamin A, vitamin C, vitamin E, co-enzyme Q, urea (particularly 1-30%), allantoin (particularly 0.1-1%), benzoyl peroxide (5-10%) menthol, lecithin, salicylic acid (particularly 0.5-10%), pantheriol (particularly 0.5-5%), and antibiotics, especially erythromycin base (1-5%), clindamycin phosphate (1-5%) and tetracycline hydrochloride (1-5%), the amounts specified in

parentheses being particularly suitable, but non-limiting, amounts by weight for such formulations.

The following non-limiting Examples serve to further illustrate the present invention. The percentage amounts referred to are by weight.

Example 1

An ointment consisting of:

Eucerine	30%
Glycerol	60%
Compound of formula (I)	10%

The ointment was prepared as follows. The compound of formula (I) was powdered and blended with a small amount of Eucerine until homogeneous, then the remaining Eucerine and glycerol were added and the whole mixture stirred until homogeneous.

An ointment of Example 1 containing 1-methylnicotinamide chloride was applied topically for the treatment of psoriasis in a group of 7 patients. After ten days treatment with the ointment six of the patients showed a considerable improvement consisting in flattening of papula and cessation of flares. None of the patients showed any negative effects of the treatment with the ointment.

Example 2

A gel consisting of:

Methylcellulose	5%
Glycerol	12%
Water	82.5%
Compound of formula (I)	0.5%

The gel was prepared as follows. Powdered methylcellulose was added to hot water while stirring intensively. The resulting dispersion was cooled to about 6°C and blended with glycerol. Compound of formula (I) was then added and the whole mixture stirred until homogeneous.

A gel of Example 2 containing 1-methylnicotinamide citrate was applied for topical treatment of leg ulcers in a group of 5 patients. After ten days treatment all the patients showed a significant improvement consisting in accelerating of granulation and epithelisation. None of the patients showed any negative effects of the treatment with the gel.

Example 3

A gel consisting of:

Methylcellulose	5%
Glycerol	12%
Water	82.7%
Compound of formula (I)	0.3%

The gel was prepared analogously to Example 3.

A gel of Example 3 containing 1-methylnicotinamide chloride was applied for topical treatment of juvenile acne in a group of 6 patients. After treatment there was cessation of active pathological symptoms in all of the patients.

An analagous gel formulation to Examples 2 and 3 comprising polyacrylic acid, propylene glycol, ethanol, triethanolamine, paraben and demineralised water, in addition to a compound of formula (I), has also been shown to be clinically effective.

Example 4

A solution consisting of:

Ethyl alcohol	40%
Water	59.99%
Compound of formula (I)	0.01%

The solution was prepared as follows. The compound of formula (I) was dissolved in water, then ethyl alcohol was added and the resulting solution cooled to ambient temperature.

A solution of Example 4 containing 1-methylnicotinamide lactate was applied in order to prevent a recurrence of acne juvenile in the group of patients referred to in Example 3. All the patients showed a prolonged period of improvement after cessation of active pathological symptoms. None of the patients showed any negative effects of the treatment with the solution.

Example 5

The influence of topical application of 1-methylnicotinamide salts on hair loss was studied in 10 patients with alopecia areata and in 24 patients with hair loss with no particular known cause.

Patients with alopecia areata used a shampoo containing 0.5% by weight of 1-methylnicotinamide chloride either every day or every second day, and applied the gel of Example 3 twice daily. Hair regrowth was observed in 8 of the patients during the first month of treatment. In the remaining patients, although hair regrowth was not observed after one month treatment, the progression of the disease has been stopped.

The other patients with hair loss used the shampoo containing 0.5% by weight of 1-methylnicotinamide chloride daily. In all patients the progression of hair loss has been stopped; in some patients hair regrowth has been observed.

None of the patients reported adverse effects of the treatment, such as itching and skin irritation.

In addition, a surprising effect seen in conjunction with the treatment of hair loss, is that in some cases grey hair was restored to its previous natural colour; in addition, such treatment is thought to prevent hair turning grey. This use of the compounds of formula (I) as defined above represents a further aspect of the present invention.

Example 6

The influence of topical application of 1-methylnicotinamide salts on skin burns was studied in 19 patients.

The gel of Example 3 was topically applied several times a day directly to the affected area in patients with burns from UV irradiation and high temperature, as well as scalds from hot liquids. There were 15 patients with first degree burns and 4 patients with second degree burns.

In the patients with first degree burns, pain and oedema diminished within the first 24 hours, erythema resolved within 2-3 days in 11 of the patients, and in the remaining 4 patients was resolved after 6 days.

In the patients with second degree burns, the pain also diminished within the first 2 days, blisters were absorbed in 1-3 days, oedema in 2-3 days. The epithelisation process of erosions and superficial ulcerations was very quick and occurred within 7 to 14 days depending on the area.

The residual scars, which were the result of ulcer healing, were considered to be purely cosmetic, and were accepted as such by both patient and physician. No adverse effects of the treatment were noted.

In addition, similar application of the gel of Example 3 to ten patients with severe sunburn resulted in effective improvement in their condition.

Further Examples

Similarly, formulations containing the following compounds have been shown to be clinically effective in treating the skin diseases and disorders referred to above, particularly acnes and psoriasis:

1-methylnicotinic acid;

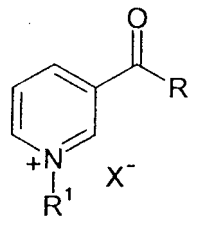
1-methylnicotinic acid ethyl ester salts;

1-methylnicotinic acid propyl ester salts.

Similarly, formulations containing 1-methyl-N'-hydroxymethylnicotinamide salts have been shown to be clinically effective in treating the skin diseases and disorders referred to above.

Claims

1. A compound of formula (I):



(I)

wherein R represents the group NR^2R^3 or the group OR^4;

R^1 represents C_{1-4} alkyl;

R^2 and R^4 each independently represent hydrogen or C_{1-4} alkyl;

R^3 represents hydrogen, C_{1-4} alkyl or CH_2OH;

and X^- is a physiologically suitable counter-anion;

for use in therapy.

2. A compound of formula (I) as defined in claim 1, for use in the preparation of a medicament for the treatment of skin diseases or disorders.

3. A compound of formula (I) as defined in claim 1, for use in the preparation of a medicament for the treatment of hair loss, sunburn, burns, scalds and for wound healing.

4. A compound of formula (I) for use as claimed in any one of claims 1 to 3 in which R^1 is ethyl or methyl, preferably methyl.

5. A compound of formula (I) for use as claimed in any one of claims 1 to 4 in which R represents the group NR^2R^3.

6. A compound of formula (I) for use as claimed in any one of claims 1 to 5 in which R^2 represents methyl or hydrogen, preferably hydrogen.

7. A compound of formula (I) for use as claimed in any one of claims 1 to 6 in which R^3 represents CH_2OH or hydrogen, preferably hydrogen.

8. A compound of formula (I) for use as claimed in any one of claims 1 to 4 in which R represents the group OR^4, and R^4 represents C_{1-4} alkyl.

9. A compound of formula (I) for use as claimed in any one of claims 1 to 4 or 8 in which R^4 represents propyl or ethyl.

10. A compound of formula (I) for use as claimed in any one of claims 1 to 7 selected from:

a 1-methylnicotinamide salt; or

a 1-methyl-N'-hydroxymethylnicotinamide salt.

11. A compound of formula (I) for use as claimed in any one of claims 1 to 4, 8 or 9 selected from:

a 1-methylnicotinic acid ethyl ester salt; or

a 1-methylnicotinic acid propyl ester salt.

12. A compound of formula (I) for use as claimed in any one of claims 1 to 4 selected from:

a 1-methylnicotinic acid salt.

13. A compound of formula (I) for use as claimed in any one of claims 1 to 12 in which the salt is a chloride, benzoate, salicylate, acetate, citrate or lactate.

14. A compound of formula (I) for use as claimed in any one of claims 1 to 4 selected from:

1-methylnicotinamide chloride;

1-methylnicotinamide citrate;

1-methylnicotinamide lactate;

1-methyl-N'-hydroxymethylnicotinamide chloride;

1-methylnicotinic acid chloride;

1-methylnicotinic acid ethyl ester chloride; or

1-methylnicotinic acid propyl ester chloride.

15. A method of treatment of a skin disease or disorder in a human or animal subject, comprising the administration to said subject of an effective amount of a compound of formula (I) as defined in any one of claims 1 or 4 to 14.

16. A method of treatment of hair loss, sunburn, burns, scalds and for wound healing in a human or animal subject, comprising the administration to said subject of an effective amount of a compound of formula (I) as defined in any one of claims 1 or 4 to 14.

17. A pharmaceutical formulation comprising a compound of formula (I) as defined in any one of claims 1 or 4 to 14 together with one or more pharmaceutically acceptable carriers, diluents or excipients.

18. A formulation as claimed in claim 17, which is for topical administration and comprises about 90 to 99.95% of a pharmaceutical base carrier and about 0.005 to about 10% by weight of the compound of formula (I).

19. A formulation as claimed in claim 18 containing about 0.01 to about 10% by weight of the compound of formula (I).

20. A formulation as claimed in claim 18 or claim 19 in the form of an ointment, gel, or aqueous solution.

INTERNATIONAL SEARCH REPORT

Int tional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/80 C07D213/82 A61K31/4406 A61K31/4425 A61K31/455
A61P17/02 A61P17/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 77, no. 3, 17 July 1972 (1972-07-17) Columbus, Ohio, US; abstract no. 14772e, page 106; XP002133576 abstract & Y. YABUHARA ET AL.: HAKKO KOGAKU ZASSHI, vol. 50, no. 2, 1972, pages 86-92, ---	1,4-7,10
X	DE 36 03 601 A (J. MAI ET AL.) 13 August 1987 (1987-08-13) claims 1,5 ---	1,3,4,8, 12
A	WO 98 52927 A (R. SCIVOLETTO) 26 November 1998 (1998-11-26) cited in the application claims ---	1-20
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2000	07/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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INTERNATIONAL SEARCH REPORT

.ernational application No.
PCT/IB 00/00019

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 15 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/IB 00/00019

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 052 705 A (J. E. BERNSTEIN) 2 June 1982 (1982-06-02) cited in the application claims	1-20
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A	EP 0 518 352 A (DAINIPPON INK AND CHEMICALS, INC.) 16 December 1992 (1992-12-16) page 25, compound N-4	1,4-7,10
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A	US 4 578 394 A (R. C. ALLEN ET AL.) 25 March 1986 (1986-03-25) column 2, compound (IV)	1,4,8
A	US 3 823 076 A (J. D. RUSHMERE) 9 July 1974 (1974-07-09) column 3, line 31 - line 54	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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